EXHIBIT I

17TH EDITION

Remington's

ALFONSO R GENNARO
Editor, and Chairman
of the Editorial Board

Pharmaceutical

Sciences

1985

MACK PUBLISHING COPMANY

Easton, Pennsylvania 18042

Library of Congress Catalog Card No 60-53334

ISBN 0-912734-03-5

The use of portions of the text of USP XX, NF XV, and USAN and the USP Dictionary of Drug Names is by permission of the USP Convention. The Convention is not responsible for any inaccuracy of quotation or for any false or misleading implication that may arise from separation of excerpts from the original context or by obsolescence resulting from publication of a supplement.

NOTICE—This text is not intended to represent, nor shall it be interpreted to be, the equivalent of or a substitute for the official United States Pharmacopeia (USP) and/or the National Formulary (NF). In the event of any difference or discrepancy between the current official USP or NF standards of strength, quality, purity, packaging and labeling for drugs and representations of them herein, the context and effect of the official compendia shall prevail.

Printed in the United States of America by the Mack Printing Company, Easton, Pennsylvania

the smaller liquid is miscible with the larger quantity of diluting liquid, the graduate may be rinsed and this loss recovered, but inconveniences are largely overcome and greater accuracy secured by the use of a pipet.

In administering small quantities of liquids, the very convenient *drop* is almost always used. It should be emphasized that *1 drop is not equivalent to 1* ♏ and that *60 drops are not equivalent to 1 fl dr*. This impression doubtless arose from the fact that 60 ordinary drops of *water* are about equal to 1 fl dr, but the volume of a drop of fluid depends on many factors, including density, temperature, viscosity, surface tension, and the size and nature of the orifice from which it is dropped. Thick viscous liquids, such as the mucilages and the syrups, necessarily produce large drops because the drop adheres to the surface of the glass as long as its weight does not overcome its power of adhesion, while chloroform, a mobile liquid, having very little adhesion to the dropping surface—produces very small drops. The greater the surface tension, the larger will be the drop, and the greater the extent of surface to which the drop adheres, the larger, proportionally, will be the drop.

A "normal" or "standard" drop measure was recommended by the Brussels Conference of 1902 for international adoption. This dropper is recognized in the USP.

Medicine Dropper

The pharmacopeial medicine dropper is 3 mm in external diameter at its delivery end, and when held vertically delivers 20 drops of water, the total weight of which is between 0.9 g and 1.1 g (at 25°). In using a medicine dropper, one should keep in mind that few medicinal liquids have the same surface and flow characteristics as water, and therefore the size of drops varies materially from one preparation to another.

When drops are specified on a prescription, the usual custom has been to employ an "eye dropper," but the standard dropper should now be supplied. It is particularly important to use the standard or a specially calibrated dropper for administering potent medicines when accuracy is required.

A standard teaspoon has not yet received acceptance.

Teaspoon

Agreement has not been reached on a standard official teaspoon, in spite of the need for such a standard measure in connection with compounding and labeling liquid medicines. For household purposes, an American Standard Teaspoon has been established by the American National Standards Institute* as containing 4.93 ± 0.24 mL. In view of the almost universal practice of employing teaspoons ordinarily available in the household for the administration of medicine, the teaspoon may be regarded as representing 5 mL.

It must be kept in mind that the actual volume delivered by a teaspoon of any given liquid is related to the latter's viscosity and surface tension, among other influencing factors.

The Human Factor—The human factor of carefulness is of paramount importance in every pharmaceutical operation in which accuracy is essential. The basic necessities for accurate measurement of liquids require (1) accurate technical equipment, (2) careful manipulation, (3) good vision, and (4) a steady hand.

* American National Standards Institute, 1430 Broadway, New York, NY 10018.

Density and Specific Gravity

Several terms are used to express the mass (weight) of equal volumes of different substances.

Absolute density is the ratio of the mass of an object, determined in or referred to a vacuum, at a specified temperature, to the volume of the object at the same temperature. This relationship is expressed mathematically as:

$$\frac{\text{mass in grams (in a vacuum)}}{\text{volume in milliliters}} = \text{absolute density}$$

Apparent density differs from absolute density only in that the mass of the object is determined in air, which mass is influenced by the difference in the buoyant effect of air on the object being weighed and on the standard masses (weights) used for comparison (if the object and masses are made of the same material, or have the same density, there will be no difference in the buoyant effect, and the apparent density will be identical with the absolute density).

Relative density is an expression sometimes employed to indicate the mass of 1 mL (not cc, which is very slightly different) of a standard substance, such as water, at a specified temperature, relative to water at 4°C taken as unity. Thus, at 4°C the relative density of water is 1.0000, while its absolute density at the same temperature is 0.999973.* To convert a relative density of water to absolute density, the former should be multiplied by 0.999973.

Specific gravity may be defined as the ratio of the mass of a substance to the mass of an equal volume of another substance taken as the standard. For gases, the standard may be hydrogen or air; for liquids and solids, it is water. From what has been stated, it is obvious that in a determination of specific gravity there will be, in general, a difference in the result if the masses (weights) are determined in air or in vacuum; if determined in, or referred to, a vacuum, the result is a *true specific gravity* (sometimes called *absolute specific gravity*), while if the masses are determined in air, the calculated result is an *apparent specific gravity*. The difference between these specific gravities is, as a rule, very small. A very important variable in specific gravity determinations is temperature, and this is doubly important because both the temperature of the substance under examination and the temperature of the standard may be different. The common practice with regard to the determination of specific gravity is that defined by the USP as follows:

Unless otherwise stated, the specific gravity basis is 25°/25°, i.e., the ratio of the weight of a substance in air at 25° to that of an equal volume of water at the same temperature.

But it is not always convenient, or desirable, to determine the weight of both the substance and the water at 25°, or even to determine the weight of the substance at the same temperature as that at which the water is weighed. Thus, the substance may be weighed at 25°, and compared with the weight of an equal volume of water at 4°, in which case the specific gravity is reported as being on a 25°/4° basis; in the case of theobroma oil, which is solid at 25°, the specific gravity is determined on a 100°/25° basis, and for alcohol it is determined on a 15.56°/15.56° basis because many years ago the US Government adopted 60°F (15.56°C) as the temperature at which alcoholometric measurements are to be made in connection with the Government's control of alcoholic liquids.

It is apparent that a completely informative statement of specific gravity must indicate the temperature of the substance under examination, as well as that of the equal volume of water (the temperatures are commonly shown as a ratio, with the temperature of the water always being indicated in the denominator). Furthermore, it should be stated whether

* Water attains its maximum absolute density of 0.999973 at 3.98°C.

several days, until the pectins which are naturally present are destroyed by enzymatic action, as indicated by the filtered juice yielding a clear solution with alcohol. Pectins, if allowed to remain, would cause precipitation in the final syrup.

Cherry Juice is described in the USP, and Raspberry Juice in USP XVIII. Concentrated Raspberry Juice BPC is prepared from the clarified juice of raspberries. Pectinase is stirred into pulped raspberries and the mixture is allowed to stand for 12 hours. The pulp is pressed, the juice is clarified, and sufficient sucrose is added to adjust the weight per mL at 20° to 1.050–1.060 g. The juice is then concentrated to one-sixth of its original volume. Sufficient sulfurous acid or sodium metabisulfite is added to preserve the juice.

Artificial flavors have now replaced many of the natural fruit juices. Although they lack the flavor of the natural juice, they are more stable and are easier to incorporate into the final pharmaceutical form.

Recent information on cranberry juice indicates that it may be effective in controlling some urinary tract infections and urolithiasis.

Nasal Solutions

Nasal solutions are usually aqueous solutions which are designed to be administered to the nasal passages in drops or spray form. While many of the drugs are administered for their local sympathomimetic effect such as Ephedrine Sulfate or Naphazoline Hydrochloride Nasal Solution, to reduce nasal congestion, a few other official preparations, Lypressin Nasal Solution and Oxytocin Nasal Solution are administered in spray form for systemic effect for the treatment of diabetes insipidus and *milk let down* prior to breast feeding, respectively.

Nasal solutions are prepared in such a way that they are similar in many respects to nasal secretions so that normal ciliary action is maintained. Thus the aqueous nasal solutions are usually isotonic and slightly buffered to maintain a pH of 5.5 to 6.5. In addition, antimicrobial preservatives similar to those used in ophthalmic preparations, and appropriate drug stabilizers, if required, are included in the formulation.

Commercial nasal preparations, in addition to the drugs listed above also include antibiotics, antihistamines and drugs for asthma prophylaxis.

A formula for Ephedrine Nasal Drops BPC is:

Ephedrine Hydrochloride	**0.5 g**
Chlorobutanol	**0.5 g**
Sodium Chloride	**0.5 g**
Water for preparations	**to 100 mL**

Otic Solutions

These solutions are occasionally referred to as aural preparations. Other otic preparations also often include formulations such as suspensions and ointments for topical application in the ear.

The main classes of drugs used for topical administration to the ear include analgesics, eg, benzocaine; antibiotics, eg, neomycin, and anti-inflammatory agents, eg, cortisone. The USP preparations include Glycerin Otic Solution which incorporates the drugs antipyrine and benzocaine in a glycerin solvent. The Neomycin and Polymyxin B Sulfates and Cortisol Otic Solutions contain appropriate buffers, dispersants usually in an aqueous solution. These otic preparations include the main types of solvents used, namely glycerin or water. The viscous glycerin vehicle, permits the drug to remain in the ear for a long time. Anhydrous glycerin being hygroscopic tends to remove moisture from surrounding tissues thus reducing swelling.

In order to provide sufficient time for aqueous preparations to act, it is necessary for the patient to remain on his side for a few minutes so the drops do not run out of the ear. Otic preparations are dispensed in a container which permits the administration of drops.

Sweet or Other Viscid Aqueous Solutions

Solutions which are sweet or viscid include Syrups, Honeys, Mucilages, and Jellies. All of these preparations are viscous liquids or semisolids. The basic sweet or viscid substances giving body to these preparations are sugars, polyols, or polysaccharides (gums).

Syrups

Syrups are concentrated solutions of a sugar such as sucrose in water or other aqueous liquid. When Purified Water alone is used in making the solution of sucrose, the preparation is known as *Syrup*, or *simple syrup*. In addition to sucrose, certain other polyols, such as glycerin or sorbitol, may be added to retard crystallization of sucrose or to increase the solubility of added ingredients. Alcohol is often included as a preservative and also as a solvent for flavors; further resistance to microbial attack can be enhanced by incorporating antimicrobial agents. When the aqueous preparation contains some added medicinal substance, the syrup is called a *medicated* syrup. A *flavored* syrup is one which is usually not medicated, but which contains various aromatic or pleasantly flavored substances and is intended to be used as a vehicle or flavor for prescriptions.

Flavored syrups offer unusual opportunities as vehicles in extemporaneous compounding and are readily accepted by both children and adults. Because they contain no or very little alcohol, they are vehicles of choice for many of the drugs that are prescribed by pediatricians. Their lack of alcohol makes them superior solvents for water-soluble substances. However sucrose based medicines continuously administered to children apparently cause an increase in dental caries and gingivitis; consequently, alternate formulations of the drug either unsweetened or sweetened with non-cariogenic substances should be considered. A knowledge of the sugar content of liquid medicines is useful for patients who are on a restricted calorie intake; such a list may be found in the literature[6].

Syrups possess remarkable masking properties for bitter and saline drugs. Glycyrrhiza Syrup has been recommended for disguising the salty taste of bromides, iodides, and chlorides. This has been attributed to its colloidal character and to its double sweetness—the immediate sweetness of the sugar and the lingering sweetness of the glycyrrhizin. This syrup is also of value in masking bitterness in preparations containing the B complex vitamins. Acacia Syrup, because of its colloidal character, is of particular value as a vehicle for masking the disagreeable taste of many medicaments. Raspberry Syrup is one of the most efficient flavoring agents and is especially useful in masking the taste of bitter drugs. Many factors, however, enter into the choice of a suitable flavoring agent. Literature reports are often contradictory and there appears to be no substitute for the taste panel. The literature on this subject has been reviewed by Meer,[7] and this reference and Chapter 68 should be consulted for further information on the flavoring of pharmaceuticals and the preparation of a number of official syrups. A series of papers is